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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/475,784	06/07/1995	PHILIP O. LIVINGSTON	43016-C/JPW/	4174

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/475,784	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *102,103,108,109 and 111-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *102,103,108,109 and 111-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed Dec. 15, 2003 is acknowledged. Claims 103-107 and 110 were canceled.

2. Claims 102, 103, 108, 109 and 111-124 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The objection to the disclosure is withdrawn in view of the submission of a new Figure 6B, which overcomes the objection.

5. The provisional rejection of claims 101-125 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 123-146 of copending Application No. 08/477,147 is withdrawn in view of the terminal disclaimer filed 12/15/2003.

6. The rejection of claims 104-106 and 125 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment canceling these claims. For clarification of the record it is noted that in the amendment filed 12/15/2003, applicants indicated an amendment to claim 124 and then a second "claim 124" that was canceled. The second "claim 124" is assumed to be a typographical error, and is interpreted to mean that claim 125 was canceled.

7. The rejection of claims 101-111 under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is withdrawn. However, see new grounds of rejection.

8. The rejection of claims 101, 111-114 and 116-125 under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is withdrawn. However, see new grounds of rejection.

9. The rejection of claims 114 and 115 under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al

(J Biochem, 79(6):1253-1261, 1976) as applied to claims 78, 80-92, 94 and 96-99 above and further in view of Diatlovitskaia et al. (Biokhimiia, 56(3): 560-564, 1991, Mar.; Abstract only) is withdrawn. However, see new grounds of rejection.

New Grounds of Rejection:

10. Claims 101, and 111 are objected to because they do not end in a "period" and therefore are not complete sentences. Also, these claims appear to be incomplete because they end with the word "and". Appropriate correction is required.

11. Claims 101, 102, 108, 109, 111-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification does not support the genus of conjugates comprising a GD3 lactone ganglioside having an "altered ceramide portion comprising an altered spingosine base".

The claimed inventions read on compositions comprising GD3 lactone ganglioside conjugates and methods of treatment comprising the administration of compositions comprising GD3 lactone ganglioside conjugates, where the ganglioside portions of the conjugates are so broadly claimed that they are not adequately described by the specification. Specifically, the recitation "GD3 lacton ganglioside derivative" that comprises "an altered ceramide portion comprising an altered sphingosine base" refers to a genus of compounds that is not supported by

the specification. The only example of an "altered ceramide portion comprising an altered spingosine base" provided by the specification is the one example of a ganglioside conjugate in which, prior to conjugation, the sphingosine base has been cleaved with ozone and reduced to form a reactive aldehyde at the C-4 carbon of the sphingosine base. This one example is not representative all the possible species encompassed by the phrase "ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising an altered sphingosine base". Therefore, the genus of conjugates is not supported by an adequate written description of the varied members of the genus, and one of skill in the art would not find that applicant was in possession of the genus of claimed compositions or claimed methods using the claimed compositions at the time of filing.

12. Claims 101, 102, 108, 109, 111-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 101, 113 and 114 are indefinite because of the recitation "saponin derivable from the bark of a Quillaja saponaria Molina tree".

Claims 102 and 111 are indefinite because of the recitation "QS-21".

The claimed inventions are indefinite because the specification does not describe with sufficient clarity the chemical and structural nature of a "saponin derivable from the bark of a Quillaja saponaria Molina tree" or of "QS-21". The specification appears to define the saponins by teaching that QS-21 is an example of one of the saponins and to reference literature that teaches one how to isolate QS-21 from a mixture of saponins. However, because the saponins or

QS-21 appear to be essential ingredients of the claimed inventions, the attempt to describe QS-21 and how it is isolated is an attempt at incorporation by reference of matter essential to the practice of the claimed inventions. However, the references cited are not available for incorporation by reference because they are non-patent publications.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim 111 is indefinite because the phrase "the saponin" lacks antecedent basis.

13. Claims 101, 102, 113, 114 and 116-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Jennings (U.S. Patent 4,356,170; issued 1982), in view of Neurath (U.S. Patent 4,591,552; issued 5/27/1986), in view of Ratcliff (U.S. Patent 5,344,870; issued 9/6/1994; effective filing 11/30/1988), in view of Patrick (U.S. Patent 4,652,629; issued 3/24/1987), in view of Blincko (U.S. Patent 5,256,409; issued 10/26/1993; effective filing 1/25/1991), in view of Marciani (supra), in view of Tsuchida (Journal of the National Cancer Institute, 78: 45-54,

1987), in view of Ritter (1991 of record) and further in view of Livingston (Proc. Natl. Acad. Sci. USA, 84: 2911-2915, 1987).

Wiegand teaches glycoconjugates comprising gangliosides conjugated to carrier proteins, wherein the ganglioside has been ozonolyzed and reduced at the C-4 double-bond of the sphingosine base to produce a reactive aldehyde intermediate that may be reacted directly with free amines present in carrier proteins to form a conjugate (col. 1, line 11- col. 2, line 44), wherein the ganglioside may be GM3, GD3, GM2 or GM1. Wiegand teaches that the coupling of gangliosides to carrier proteins is appropriate of all gangliosides. Wiegand teaches that glycoconjugates of gangliosides are useful as vaccines (col. 1, lines 50-55). Wiegand fails to explicitly teach that the bond between the aldehyde group of the ozonolyzed and reduced ganglioside and the carrier protein would be via a lysine residue of the carrier protein. However, as evidenced by Jennings, the chemistry of linking a carbohydrate containing a reactive aldehyde group to a carrier protein is well known and likely would be via a lysine (see col. 3, lines 40-46 and claims 11 and 18 at cols. 9 and 10, respectively). Additionaly, Wiegand fails to specifically teach a glycoconjugate comprising the specific carrier protein, KLH, and fails to teach a glycoconjugate having a ganglioside to KLH molar ratio of about 200:1 to about 1400:1. However, with regard to novelty and unobviousness of KLH as a carrier protein, before the filing date of the parents of the instant application, KLH was known as a useful carrier protein for carbohydrate antigens (see Ratcliff, col. 29, lines 46-51); for small peptide antigens (see Patrick, col. 9, lines 7-28); and for tricyclic antidepressant drugs (see Blincko, col. 7, lines 29-41). Additionally, Ritter suggests the desirability of conjugating gangliosides to KLH: Ritter teaches that covalent attachment to KLH results in the production of IgG antibodies in melanoma

patients, and that the production of IgG antibodies is desirable because IgG antibodies are of higher affinity, better able to penetrate solid tissues, able to mediate antibody-dependent cell-mediated cytotoxicity and remains in the circulation for longer periods after immunization (see page 106, first col).

With regard to the molar ratios of the GD3 lactone glycoconjugate, applicants have argued that Wiegand teaches away from a glycoconjugate having a ganglioside: Keyhole Limpet Hemocyanin molar ratio that is from 200:1 to 1400:1, because Wiegand's molar ratio is 16-18: 1 with HSA as the carrier protein. This argument is not found persuasive because the example in Wiegand pointed to by applicants is one using a different carrier protein from what is claimed. A different carrier protein will likely have a different number of lysyl amino groups than does KLH. Applicants have failed to demonstrate that achieving such a molar ratio when the carrier protein is KLH is an unexpected result, and applicants have failed to demonstrate that Wiegand teaches away from the use of KLH as a carrier protein. Wiegand teaches conjugates obtained by either a direct conjugation procedure where ganglioside having a reactive aldehyde group is reacted with lysyl amino groups on the carrier protein, and also teaches a conjugation procedure where free amino groups (provided by lysine side chains) of the carrier protein are first reacted with SPDP. With either method, the number of lysyl amino groups would determine the maximum possible number of haptens that may be conjugated to the carrier protein. In the case of HSA, this reaction procedure appears to result in a conjugation ratio of 16-18 molecules of ganglioside per HSA. However, Neurath, using KLH as the carrier protein and the SPDP heterobifunctional linker method of Wiegand, teaches peptide-KLH conjugates that contain approximately 200 peptide molecules per KLH (see col. 17, lines 5-40). Therefore, it would

have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the conjugates of the claimed compositions, where the conjugates comprise a GM2 ganglioside covalently bound to via lysine residues of KLH, a well known carrier protein, by reductive amination as taught by Jennings, and to have achieved a ganglioside-KLH molar ratio of between 200:1 to 1400:1, because the Neurath teaches that a molar ratio of hapten to carrier protein of 200:1 can be achieved using KLH and using a method that attaches the hapten to KLH via lysine residues. The fact that Wiegand's molar ratio is lower than that of the claimed conjugates appears to be due to the difference in carrier protein used.

Wiegand fails to teach a glycoconjugate within a composition containing a saponin. However, Marciani teaches the use of 20 ug of QS-21 as an adjuvant in a genetically-engineered subunit vaccine against feline leukemia virus, and teaches that the choice of QS-21 was important in achieving an immunogenic response to the recombinant viral peptide in that QS-21 was much more effective than alum or oil emulsions in eliciting a humoral response and were protected from viral challenge (page 94, 2nd col., 2nd full para to page 95, 1st col). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have used an adjuvant such as QS-21, because QS-21 appears to be superior to other art known adjuvants such as alum and oil emulsions.

Although Wiegand teaches a glycoconjugate that comprises a GD3 ganglioside, Wiegand fails to teach a glycoconjugate comprising GD3 lactone. However, Tsuchida teaches that GD3 is expressed in all of the human melanoma samples tested and Ritter teaches that a GD3-lactone (GD3, lactone I) induces antibodies that cross-react with GD3, and is the preferable antigen for use in a vaccine against melanoma cells that express GD3. Therefore, it would have been prima

facie obvious to one of ordinary skill in the art at the time the invention was made to have used gangliosides other than that of GM2, such as GD3-lactone, because Tsuchida GD3 is a major ganglioside of melanoma cells and because Ritter teaches that GD3 lactone induces antibodies that cross-react with GD3. Wiegand also fails to teach the specific range of amounts of conjugated ganglioside in a composition, where the amounts are about 1 ug to about 200 ug. However, Livingston teaches immunization of human melanoma patients with a dose of 100 ug of an unconjugated GM2 ganglioside preparation (combined with BCG or S. minnesota mutant R595) that produced an antibody response (see page 2912, 2nd col. – page 2913, and Table 2). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have determined the appropriate amounts of a KLH-conjugated ganglioside to administer.

The claimed inventions are also drawn to methods of treatment, either a method of stimulating or enhancing production of an antibody to GD3 lactone or a method of treating a human subject having cancer, comprising the administration of compositions comprising GD3 lactone ganglioside conjugates. Wiegand suggests such methods because Weigand teaches that ganglioside conjugates may be used as vaccines. Additionally, Livingston and Ritter both teach that melanoma patients respond to preparations comprising gangliosides and adjuvants by producing ganglioside and melanoma specific antibodies. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to use the ganglioside compositions comprising a conjugate of Weigand where the carrier protein is KLH, as suggested by Ritter (and also Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods of treatment for the production of antibodies to gangliosides, or for the treatment of a

human subject having cancer. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is well within the skill of the ordinary artisan.

14. Claims 114 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Jennings (U.S. Patent 4,356,170; issued 1982), in view of Neurath (U.S. Patent 4,591,552; issued 5/27/1986), in view of Ratcliff (U.S. Patent 5,344,870; issued 9/6/1994; effective filing 11/30/1988), in view of Patrick (U.S. Patent 4,652,629; issued 3/24/1987), in view of Blincko (U.S. Patent 5,256,409; issued 10/26/1993; effective filing 1/25/1991), in view of Marciani (supra), in view of Tsuchida (Journal of the National Cancer Institute, 78: 45-54, 1987), in view of Ritter (1991 of record) in view of Livingston (Proc. Natl. Acad. Sci. USA, 84: 2911-2915, 1987) and further in view of Diatlovitskaia et al. (Biokhimiia, 56(3): 560-564, 1991, Mar.; Abstract only).

The claimed inventions also read on methods of treatment of tumors of epithelial origin. The teachings of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Tsuchida, Ritter and Livingston are set forth above. The combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Tsuchida, Ritter and Livingston fail to teach treating a cancer of epithelial origin. However, Diatlovitskaia teaches that the ganglioside GD3 is over-expressed breast carcinomas, which is an example of a cancer of epithelial origin. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the ganglioside compositions comprising a conjugate of Weigand where the

ganglioside was a GD3-lactone (which Ritter teaches allows production of antibodies specific for GD3) where the carrier protein is KLH, as suggested by Ritter (and also Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods for the treatment of a human subject having an epithelial cancer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached at (571) 272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
April 14, 2004

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